REMARKS

Applicants are submitting this amendment after final rejection pursuant to 37 CFR 1.116 because they believe that all claims now presented are in condition for allowance. In any event entry of this amendment will place the case in better form for appeal. Applicants have raised no new issues and added no new matter to this application. Finally the amendments and arguments that Applicants have made herein are in direct response to points raised by the Examiner in the last office action and Applicants could not have filed their response at an earlier date.

Applicants have amended claims 29, 31, 33, 35, 37 and 39, canceled claims 30, 32, 34, 36, and 38, and added new claims 40 and 41. The amendments to claims 29, 31, 33, 37 and 39 merely change the style of the claims according to the suggestions of the Examining Attorney on pages 2 and 3 of the office action. For the most part the amendments to claim 35 reflect the Examiner's interpretation of the claim as set forth on page 5 of the office action. Claim 35 as now presented is directed to a recombinant Corynebacterium wherein the L-serine dehydratase sdaA gene having SEQ ID NO: 1 undergoes completion deletion of nucleotides 506 through 918. No longer does claim 35 cover a recombinant Corynebacterium where less than all of the nucleotides 506 through 918 are deleted. Furthermore Applicants have combined claims 35 and 36 so that the recombinant Corynebacterium now covered does not

express L-serine dehydratase sdaA at all. For antecedent basis see especially page 5, line 14 to page 6, line 21, and in Example 4, Table 2 on page 31 of the specification.

Applicants have also added new claims 40 and 41 also directed to recombinant Corynebacteria, that do not express L-serine dehydratase at all. Claim 40, like claim 35, is directed to a recombinant Corynebacterium wherein the L-serine dehydratase sdaA gene having SEQ ID NO: 1 undergoes completion deletion of nucleotides 506 through 918. However, claim 40 requires at the end that the recombinant Corynebacterium now covered does not express L-serine dehydratase at all, rather than L-serine dehydratase sdaA at all. See page 6, lines 11 through 21, page 15, lines 9 through 14, and Example 4, Table 2 for antecedent basis. Applicants point out that it is known in the art that among some microorganisms, such as E Coli, that L-serine dehydratase (sdaA) is not necessarily the only nucleic acid that expresses L-serine dehydratase. See Zhang et al, "Deficiency in L-serine deaminase results in abnormal growth and cell division of Escherichia coli K-12"; Molecular Microbiology, (2008), 69(4), pp 870 to 881 (2008).

The Zhang et al publication indicates that in some microorganisms, such as E Coli, there are three genes that have L-serine deaminase activity (another name for L-serine dehydratase, see the excerpt from Wikipedia), and that those three genes include sdaA, sdaB and tcdG. See the abstract of Zhang et al. According to page 6, lines 11 through 21, page 15, lines 9 through 14, and

Example 4, Table 2, the recombinant microorganisms according to the present invention may be entirely devoid of all L-serine dehydratase activity and as established by Zhang et al expression of the sdaA gene in some organisms, such as E Coli, is not the only source of L-serine dehydratase activity. While it is now known following the Applicants' present invention that sdaA is the only gene expressing L-serine dehydratase in Corynebacteria, that fact was not known at the time of the Applicants' filing of the German priority application or of the Applicants' International filing date. The significance of this aspect of the Applicants' invention will be discussed further at the end of this amendment.

Claim 41 is directed to a different aspect of the present invention. Claim 41 is directed to a recombinant Corynebacterium where the entire L-serine dehydratase (sdaA) gene having SEQ ID NO: 1 is deleted from the microorganism, not just nucleotides 506 through 918. See page 6, lines 11 through 21 of the specification for antecedent basis.

Thus claims 29, 31, 33, 35, 37, and 39 through 41 are now in the case and are presented for examination.

The Examiner has rejected all claims last presented with respect to the wording of the claims, in particular whether the wording of the claims is sufficiently definite as required by 35 USC 112, second paragraph, and whether the claims as presently in the case are supported by a specification that adequately describes the invention as required by the first paragraph of 35 USC 112.

The Examiner has also rejected all claims last presented as obvious under 35 USC 103 arguing that no claim is patentably distinguishable over the combination of the KUBOTA reference appearing in Agric. Biol. Chem., 49(1), pp 7 through 12 (1985) and US Published Patent Application 2002/0197605 A1 to NAKAGAWA et al.

On pages 2 through 5 of the office action the Examiner sets forth a number of reasons why he believes that the claims are indefinite and need further clarification. The Examiner has provided a number of suggestions on how to render the claims more definite. There are two principal kinds of changes that the Examiner requires. The Examiner has first of all has drawn a sharp distinction between (1) changing the coding of the nucleic acid of SEQ ID NO: 1 which can express an L-serine dehydratase that has reduced activity in terms of degrading L-serine to pyruvate and (2) modifying a promoter region upstream of the nucleic acid that codes for L-serine dehydratase so that by modifying the promoter region the level of expression of the coding region that expresses the L-serine dehydratase is changed.

While both methods are disclosed in the specification as a way to limit the ability of the L-serine dehydratase to catalyze the decomposition of L-serine to pyruvate, from reading the examples, the presently claimed invention is more directed to ways for limiting the decomposition of L-serine through limiting the enzymatic activity of the L-serine dehydratase encoded by the modified polynucleotide of SEQ ID NO: 1, especially where the

polynucleotides from position 506 to position 918 have been deleted. See especially Examples 2 and 4. Applicants have not any specific examples or any other specific details that relate to modifications in the promoter region upstream of the region coding for L-serine dehydratase to limit expression of that nucleic acid. According to page 4, central paragraph of the office action, the Examiner insists that Applicants make it clear that the present invention relates to limiting L-serine decomposition by making molecular modifications in the polynucleotide that expresses L-serine dehydratase and not in changes in the promoter region that controls the level of expression of the L-serine dehydratase.

Applicants agree that the specific features of the presently claimed invention relate to changes in the polynucleotide that expresses L-serine dehydratase and not in changes in the promoter region that controls the level of expression of the L-serine dehydratase. Applicants emphasize, however, that it is also possible to make changes in the coding region of the polynucleotide that codes for L-serine dehydratase that do more than just influence the activity of the L-serine dehydratase expressed. In fact, changes in the coding region of the polynucleotide that expresses L-serine dehydratase may influence the expression level of the L-serine dehydratase or the rate of formation of L-serine.

The Examiner is aware that Applicants have defined in the claims last presented their changes in the coding sequence for SEQ ID NO: 1 that codes for L-serine dehydratase as a coding sequence

that either deletes all of the nucleotides from position 506 to position 918, or only some of the nucleotides, or that could include a mutation within this region of the polynucleotide coding for L-serine dehydratase. The Examiner, however, believes that the specification inadequately supports this aspect of the invention as broadly claimed and that all that the specification really supports is the L-serine dehydratase that is coded for in the SEQ ID NO: 1 according to the present invention which is a modified SEQ ID NO: 1 where all of the nucleotides from position 506 to position 918 are deleted. See the central paragraph of page 7 of the office action. Here the Examiner argues pursuant to the first paragraph of 35 USC 112 that the specification does not adequately define the invention and that the inventors are not in possession of the invention beyond deleting all of the nucleotides 506 to 918 from SEQ ID NO: 1.

The Examiner has also made the analogous argument with respect to enablement under the first paragraph of 35 USC 112. See the paragraph bridging pages 8 and 9 of the office action. Here the Examiner argues that the specification enables one to obtain L-serine dehydratase of SEQ ID NO: 2 with reduced activity for degrading L-serine to pyruvate, if the polynucleotide of SEQ ID NO: 1 is modified to delete all of the nucleotides from position 506 to position 918. Now that Applicants have amended the claims so that the claims are directed to nucleic acids having SEQ ID NO: 1 where all of the nucleotides from position 506 to position 918 are

deleted, the issues set forth questioning the sufficiency of the disclosure no longer apply.

Applicants have combined claims 35 and 36 into claim 35 and have canceled claims 36 and 38. Another issue that the Examiner raises is whether the Applicants need both claims 36 and 38 as last presented. The flanking sequences do not remain in the microorganism after recombination; those sequences are removed and so Applicants have canceled claim 38.

Applicants have combined claims 35 and 36 into new claim 35 because one of the most important aspects of the present invention is that deletion of nucleotides from position 506 to position 918 results in a recombinant Corynebacterium that does not express an L-serine dehydratase with any enzymatic activity at all, and does not express an L-serine dehydratase with just reduced enzymatic activity. See the data in Table 2 in Example 4 for antecedent basis.

Applicants also regard one of the most important aspects of this invention as the deletion in its entirety of the polynucleotide of SEQ ID NO: 1, not just the deletion of the nucleotides from position 506 to position 918. That is why the Applicants have added new claim 41. See page 6, lines 11 through 21 of the specification for antecedent basis. The recombinant Corynebacterium of claim 41 does not express an L-serine dehydratase with any enzymatic activity at all.

There is the matter of the obviousness of all of the claims submitted in view of the combination of KUBOTA and NAKAGAWA et al. The Examiner indicates in the paragraph bridging pages 12 and 13 that it would be obvious to those "skilled in the art" from the combination of these two references to delete some or all of the polynucleotide of SEQ ID NO: 1 to obtain a recombinant Corynebacterium with either less ability to degrade L-serine to pyruvate or no ability at all to degrade L-serine to pyruvate, especially if the entire L-serine dehydratase gene of SEQ ID NO: 1 is deleted. The Examiner is not at al, convinced by Applicants' arguments that the NAKAGAWA et al reference does not actually test the polynucleotide of SEQ ID NO: 1 to see if it has L-serine dehydratase activity and that the combination of NAKAGAWA et al with KUBOTA must fail. Instead the Examiner argues that KUBOTA identifies the function of L-serine dehydratase and NAKAGAWA et al identifies the structure of L-serine dehydratase and so it would be obvious from these two references to delete the L-serine dehydratase in part or completely to arrive at the present invention.

Applicants are claiming two deletion mutant Corynebacteria, one in claims 35, 37 and 40 where, specifically the deletion from SEQ ID: NO: 1 of the nucleotides 506 through 918, and the other in claim 41 with the complete deletion of SEQ ID NO:. 1. Applicants regard the invention claimed in claims 29, 31, 33 and 39 as claims more related to the first deletion mutant because these

claims are directed to the isolated nucleotide SEQ ID NO: 1 where the nucleotides 506 through 918 have been deleted, vectors containing such a polynucleotide, and primers used in the preparation of SEQ ID NO: 1 where the nucleotides 506 through 918 have been deleted. The deletion mutants of claims 35, 37 and 40 are recombinant Corynebacteria in which the polynucleotide of SEQ ID NO: 1 with the nucleotides 506 through 918 deleted, has been introduced. In the case of the deletion mutant of claim 41, the entire polynucleotide of SEQ ID NO: 1 has been deleted from the recombinant Corynebacterium. The Examiner objects that there is no inventive step because both the structure and the function of the serine dehydratase are disclosed according to the prior art. The Examiner requires reasons that establish an inventive step for both embodiments.

Applicants will first address the partial deletion with the segments 506 through 918 from SEQ ID NO: 1. This partial deletion results in complete inactivity of the serine dehydratase as evidenced by the data in Example 4, Table 2.

For one skilled in the art it is entirely surprising that the partial deletion leads to complete inactivity of the serine dehydratase. Within the entire enzyme structure in many cases there are sequence segments whose deletion has no effect at all on the function of the enzyme. For instance, this is the case for regulatory domains, which have no effect on enzyme activity. Prior to the Applicants' invention, it could not be foreseen what the

case would be when Applicants deleted nucleotides 506 through 918 from SEQ ID NO: 1. It was by no means obvious that deleting segments 506 through 918 would lead to complete inactivation of the serine dehydratase because deletion of that one particular sequence segment might not have had a significant effect on the function of the enzyme. For this reason it is surprising that this partial deletion has an effect on the activity of the serine dehydratase and in particular that the enzyme activity is zero after this partial deletion. The Examiner's argument therefore lacks support in that there is no suggestion in the art, including KUBOTA, NAKAGAWA et al, or the two in combination that deletion of nucleotides 506 through 918 would result in complete deactivation of the L-serine dehydratase (sdaA). Therefore, from Applicants' perspective, claims 29, 31, 33, 35, 37, 39 and 40 are patentably distinguishable over the prior art.

With regard to the complete deletion of SEQ ID NO: 1 from the recombinant Corynebacterium of claim 41, Applicants assert the following: Although Applicants have not provided an example for the complete deletion of SEQ ID NO: 1 from a recombinant microorganism, in light of the fact that deletion of only nucleotides 506 through 918 from that sequence leads to serine dehydratase activity being switched off completely as established in Example 4, it is obvious that complete deletion of SEQ ID NO: 1 also leads to complete elimination of serine dehydratase activity. Therefore L-serine does not decompose, either, because this enzyme

activity is switched off. Again, the Examiner argues that with the given structure and function of L-serine dehydratase of SEQ ID NO: 1, it was obvious to one skilled in the art that the complete elimination of SEQ ID NO: 1 from the recombinant Corynebacteria would result in completely switching off the decomposition of L-serine based on this enzymatic degradation function. This appraisal by the Examiner is incorrect. The Examiner's argument that total elimination of SEQ ID NO: 1 from the recombinant microorganism would obviously lead to a complete switching off of L-serine enzymatic degradation presupposes that the recombinant Corynebacterium of claim 41 has merely one serine dehydratase, and one gene coding for it, namely, sdaA. However, as of the date of the Applicants' claimed invention (priority date) and as of the International Filing Date, these facts were not known in the art. It is known today only because of the results of the Applicants' present invention. On the contrary, it is also known that numerous organisms (e.g. E Coli) include a plurality of functionally equivalent enzymes, for instance a plurality of serine dehydratases and genes coding for them. See the Zhang et al reference. Thus switching off with respect to complete deletion of a gene coding for serine dehydratase is by no means a reason for why no serine dehydratase activity should be present inside the organism at all.

In Example 4 Applicants presented Table 2 on page 31 of the application with experimental results that demonstrate that the serine dehydratase is completely switched off. Although these data

relate to a recombinant Corynebacterium where the L-serine dehydratase of SEQ ID NO: 1 has only been partially deleted, that is nucleotides 506 through 918, for the reasons cited above expanding to complete deletion of this gene is permissible because if partial deletion leads to inactivity, complete deletion of this gene also leads to inactivity. Because according to these experimental results no serine dehydratase activity at all is detected in the organism, that is, serine dehydratase activity is zero, it is evident that the L-serine dehydratase (sdaA) is the only serine dehydratase in the recombinant Corynebacteria, which is not obvious, as stated above, because many microorganisms contain a plurality of functionally equivalent enzymes. Again see Zhang et al, "Deficiency in L-serine deaminase results in abnormal growth and cell division of Escherichia coli K-12"; Molecular Microbiology, 69(4), pp 870 to 881 (2008). Note from the abstract of this reference that E Coli contain three genes that code for L-serine deaminase (i.e. L-serine dehydratase), namely, sdaA, sdaB and tcdG. Therefore it is known in the art that in microorganisms one particular gene such as sdaA may not be the only gene that codes for L-serine dehydratase. Thus it was also surprising that complete deletion alone of the sdaA gene coding for the serine dehydratase according to SEQ ID NO: 1 leads to completely switching off the serine dehydratase function in the corresponding organism. For this reason Applicants' very good results from completely switching off the serine dehydratase activity in the recombinant

Corynebacteria of claim 41 as well as of claims 35, 37 and 40 were not to be expected.

Applicants believe that all claims now presented are in condition for allowance and earnestly solicit a response to that effect.

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